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07/202,869	06/03/88	HOROSZEWICZ	8455.102

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EXAMINER	
HUTZELL, P	
ART UNIT	PAPER NUMBER
186	3

DATE MAILED: 03/01/90

This is a communication from the examiner in charge of your application.

COMMISSIONER OF PATENTS AND TRADEMARKS

[X] This application has been examined [ ] Responsive to communication filed on _____ [ ] This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), 0 days from the date of this letter. Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. [X] Notice of References Cited by Examiner, PTO-892.
2. [X] Notice re Patent Drawing, PTO-948.
3. [ ] Notice of Art Cited by Applicant, PTO-1449
4. [ ] Notice of Informal Patent Application, Form PTO-152
5. [ ] Information on How to Effect Drawing Changes, PTO-1474
6. [ ] _____

Part II SUMMARY OF ACTION

1. [X] Claims 1-42 are pending in the application.
   Of the above, claims 25, 27, 32-42 are withdrawn from consideration.
2. [ ] Claims _____ have been cancelled.
3. [ ] Claims _____ are allowed.
4. [X] Claims 1-24, 26, 28-31 are rejected.
5. [ ] Claims 10, 11, 28 are objected to.
6. [X] Claims 1-42 are subject to restriction or election requirement. Said
7. [X] This application has been filed with informal drawings which are acceptable for examination purposes until such time as allowable subject matter is indicated.
8. [ ] Allowable subject matter having been indicated, formal drawings are required in response to this Office action.
9. [ ] The corrected or substitute drawings have been received on _____. These drawings are [ ] acceptable; [ ] not acceptable (see explanation).
10. [ ] The [ ] proposed drawing correction and/or the [ ] proposed additional or substitute sheet(s) of drawings, filed on _____ has (have) been [ ] approved by the examiner. [ ] disapproved by the examiner (see explanation).
11. [ ] The proposed drawing correction, filed _____, has been [ ] approved. [ ] disapproved (see explanation). However, the Patent and Trademark Office no longer makes drawing changes. It is now applicant's responsibility to ensure that the drawings are corrected. Corrections MUST be effected in accordance with the instructions set forth on the attached letter "INFORMATION ON HOW TO EFFECT DRAWING CHANGES", PTO-1474.
12. [ ] Acknowledgment is made of the claim for priority under 35 U.S.C. 119. The certified copy has [ ] been received [ ] not been received [ ] been filed in parent application, serial no. _____; filed on _____.
13. [ ] Since this application appears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. [ ] Other

PTOL-326 (Rev. 7-82) EXAMINER'S ACTION

15. Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claims 1-31, drawn to monoclonal antibodies, processes for producing monoclonal antibodies, hybridomas and general methods for detecting prostate carcinomas, classified in Classes 530 and 435, subclasses 387, (240.21, 240.27 and 7).

II. Claims 32-39, drawn to a non-invasive competitive binding immunosorbent method for detecting prostatic carcinoma, classified in Class 435, subclass 7.

III. Claims 40 and 42, drawn to passive immunotherapy methods, classified in Class 424, subclass 85.8.

IV. Claim 41, drawn to an immunotherapy method using a cytotoxic conjugate, classified in Class 424, subclass 85.5.

The inventions are distinct, each from the other because of the following reasons:

Inventions I and II-IV are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (MPEP 806.05(h)). In the instant case the product as claimed can be used in materially different processes such as the multiple diverse methods of inventions II-IV, or coupled to a solid support for the purification of antigen.

The methods of Groups II-IV are distinct. The method of Group II is a non-invasive competitive binding immunosorbent method for detecting prostatic cancer in patients. Group III contains methods for passive immunotherapy using monoclonal antibodies and Group IV an immunotherapy method using a cytotoxic conjugate. These methods clearly differ in the method steps and parameters and in the reagents used.

Because these inventions are distinct for the reasons given above and have acquired a separate status in the art as shown by their different classification and divergent subject matter, and because the searches for the individual Groups are not coextensive, restriction for examination purposes as indicated is proper.

16. If Group I is elected a further election of species is required as follows:

This application contains claims directed to the following patentably distinct species of the claimed invention: I. a monoclonal antibody with the characteristics of 7E11-C5 and corresponding hybridoma; II. a monoclonal antibody with the characteristics of 9H10-A4 and corresponding hybridoma.

Applicant is required under 35 U.S.C. 121 to elect a single disclosed species for prosecution on the merits to which the claims shall be restricted if no generic claim is finally held to be allowable. Currently, claims 1 and 20 are generic.

Applicant is advised that a response to this requirement must

include an identification of the species that is elected consonant with this requirement, and a listing of all claims readable thereon, including any claims subsequently added. An argument that a generic claim is allowable or that all claims are generic is considered nonresponsive unless accompanied by an election.

Upon the allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which are written in dependent form or otherwise include all the limitations of an allowed generic claim as provided by 37 CFR 1.141. If claims are added after the election, applicant must indicate which are readable upon the elected species. MPEP 809.02(a).

Should applicant traverse on the ground that the species are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the species to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103 of the other invention.

During a telephone conversation with Karen Lenney on January 26, 1990 a provisional election was made with traverse to prosecute the invention of Group I, specie I, claims 1-24, 26, and 28-31. Affirmation of this election must be made by applicant in responding to this office action. Claims 25, 27 and 32-42 are

withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

17. The figures are objected to because the poor quality of the copy of Figure 2 precludes evaluation of the staining pattern of tissue using monoclonal antibody 7E11. Also, figures should be labeled Fig.1-3 for clarity. Correction is required.

18. Applicant is reminded of the proper content of an Abstract of the Disclosure.

A patent abstract is a concise statement of the technical disclosure of the patent and should include that which is new in the art to which the invention pertains.
If the patent is of a basic nature, the entire technical disclosure may be new in the art, and the abstract should be directed to the entire disclosure.

If the patent is in the nature of an improvement in an old apparatus, process, product, or composition, the abstract should include the technical disclosure of the improvement.

In certain patents, particularly those for compounds and compositions, wherein the process for making and/or the use thereof are not obvious, the abstract should set forth a process for making and/or use thereof.

If the new technical disclosure involves modifications or alternatives, the abstract should mention by way of example the preferred modification or alternative.

The abstract should not refer to purported merits or speculative applications of the invention and should not compare the invention with the prior art.

Where applicable, the abstract should include the following: (1) if a machine or apparatus, its organization and operation; (2) if an article, its method of making; (3) if a chemical compound, its identity and use; (4) if a mixture, its ingredients; (5) if a process, the steps. Extensive mechanical and design details of apparatus should not be given.

The abstract of the present application purports the claimed monoclonal antibodies to be useful therapeutically and

diagnostically, which uses are not supported in the specification. The abstract is confusing in describing the antigenic determinants recognized by the antibodies as being limited to human prostate epithelial cells and normal prostatic epithelial cells as no distinction is seen between the two cells.

19. Claims 10, 11 and 28 are objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim cannot depend from any other multiple dependent claim. In the interest of compact prosecution, each of these claims will be considered to depend on claim 1 only for the purpose of this action. However, treatment in this manner does not relieve applicant of the burden of addressing this objection in response to this office action. See 37 C.F.R. 1.111.1.

20. Claims 1-4, 7, 8, 11 and 14 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is indefinite in the recitation of " is reactive" in that it is not clear in what sense the antibody reacts with the epitope. Substitution of "which specifically binds" is suggested. Claim 2 is indefinite in the recitation of an antibody capable of "immunologically staining" prostatic epithelium in that an antibody per se does not stain cells. Claim 3 is indefinite in the recitation of "periphery" in that it is not clear as to the exact sub-cellular location of staining- cell membrane surface,

peripheral cytoplasm, etc.? Claim 3 is further indefinite in the recitation of "normal prostatic cells" in that it is not clear as to what cell types are encompassed- normal epithelium, stroma, basal cells, etc.? Claims 4 and 11 are indefinite in the recitation of "other" carcinomas in that it is not clear as to what "other" encompasses, e.g. all known types of carcinoma or a particular group of carcinomas which has been tested ? Claim 7 is indefinite in the recitation of an animal immunized with a "metastatic lesion" in that it is not clear as to what the term encompasses. For example, does the term encompass only cells or tissue directly obtained from an individual or also cultured cells lines originally established from tissues containing metastatic lesions? Claim 8 is unclear in the recitation of "the human prostatic carcinoma cells" in that the claim lacks proper antecedent basis in claim 7 from which it depends. It is not clear as to which prostatic carcinoma cells claim 8 refers. Claim 8 is further unclear in the recitation of cells "derived from" cells in that it is not clear in what sense the cells are derived. Substitution of "isolated from" or "originating from" is suggested. Claim 14 is indefinite in the recitation of "a membrane" in that the term implies a single membrane rather than specifying a membrane-enriched fraction. Claim 24 is indefinite in the recitation of "ATCC No. HB_____" in that it is not clear as to the accession number and, thus, the identity of the cell line being claimed. "Cell" in line 5 of claim 18 should be

"cells".

21. The following is a quotation of the first paragraph of 35 U.S.C. §112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The specification is objected to under 35 U.S.C. §112, first paragraph, as failing to provide support for a monoclonal antibody, as claimed in claim 1 which is specific for a non-secretory membrane-associated prostatic epithelial antigen. The specification describes a monoclonal antibody 7E11, which is specific for an antigen which does not appear to be secreted by LNCaP cultured cells. However, 7E11 is shown to immunologically react with a substance present in serum obtained from certain patients with prostatic carcinoma. Thus, it is not demonstrated that the antigen recognized by MAB 7E11 is indeed non-secretory under in vivo conditions.

22. The specification is objected to under 35 U.S.C. 112, first paragraph, as failing to provide an adequate written description of the invention, failing to provide an enabling disclosure and failing to present the best mode contemplated by an applicant for carrying out the invention without complete evidence of the deposit of the biological material.

The specification lacks complete deposit information for the deposit of the hybridoma 7E11-C5. Because it does not appear that hybridomas secreting antibodies with the chaacteristics of 7E11 are known and publicly available or can be reproducibly isolated from nature without undue experimentation and because the best mode disclosed by the specification requires the use of the monoclonal antibody 7E11, a suitable deposit for patent purposes is required. Filing of evidence of the reproducible production of the cell line and antibody or filing of evidence of a deposit is required.

Applicant's referral to the deposit of HB _____ on page 49 of the specification is an insufficient assurance that all required deposits have been made and all the conditions of M.P.E.P. 608.01(p)(c) met.

If the deposits were made under the provisions of the Budapest Treaty, filing of an affidavit or declaration by applicants assignees or a statement by an attorney of record over his or her signature and registration number stating that the deposits have been accepted by an International Depository Authority under the provisions of the Budapest Treaty, that all restrictions upon public access to the deposits will be irrevocably removed upon the grant of a patent on this application and that the deposit will be replaced if viable samples cannot be dispensed by the depository is required. This requirement is necessary when deposits are made under the

provisions of the Budapest Treaty as the Treaty leaves this specific matter to the discretion of each State. As a possible means for completing the record, applicant may submit a copy of the contract with the depository for deposit and maintenance of each deposit.

If the deposits have not been made under the provisions of the Budapest Treaty, then in order to certify that the deposits comply with the criteria set forth in M.P.E.P. 608.01(p)(c), items 1-3 regarding availability and permanency of deposits, assurance of compliance is required. Such assurance may be in the form of an affidavit or declaration by applicants or assignees or in the form of a statement by an attorney of record who has the authority and control over the conditions of deposit over his or her signature and registration number averring:

(a) during the pendency of this application, access to the deposits will be afforded to the Commissioner upon request;

(b) all restrictions upon the availability to the public of the deposited biological material will be irrevocably removed upon the granting of a patent on this application;

(c) the deposits will be maintained in a public depository for a period of at least thirty years from the date of deposit or for the enforceable life of the patent of or for a period of five years after the date of the most recent request for the furnishing of a sample of the deposited biological material, whichever is longest; and

(d) the deposits will be replaced if they should become nonviable or non-replicable.

As a possible means for completing the record, applicant may submit a copy of the contract with the depository for deposit and maintenance of each deposit.

23. Claims 1-24, 26 and 28-31 are rejected under 35 U.S.C. 112, first paragraph, for the reasons set forth in the objection to the specification.

24. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The following is a quotation of 35 U.S.C. 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

25. Claims 1-24, 26 and 28-31 are rejected under 35 U.S.C. 102(a) as being clearly anticipated by Horoszewicz et al..

The Horoszewicz et al. reference presents and ambiguity with regard to the inventorship because it is in the name of 3 co-authors, only one of which is an inventor herein. Furthermore, the reference states on page 928 that the hybridoma 7E11 was produced by S. Leong. Because of this ambiguity, it is incumbent upon applicants to provide a satisfactory showing which would lead to a reasonable conclusion that applicant alone is the inventors of the claimed invention. In re Katz, 687 F2d. 450, 215 USPQ 14 (CCPA 1982). To clear up the ambiguity, applicants may file declarations by the non-applicants setting forth the facts which provide an explanation why the non-applicants are not inventors. MPEP 715.05.

26. Claims 1-3, 10, 11 20, 28, 29 and 31 are rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103 as obvious over Frankel et al..

Claims 1-3, 10, 11, 20, 28, 29 and 31 are drawn to cell lines and corresponding monoclonal antibodies specific for a membrane-associated, non-secreted antigen of human normal and prostatic cancer epithelium, which can bind to and stain prostatic epithelium and which stains the periphery of cells heterogeneously, weakly stains normal prostatic cells and nonmalignant ductal epithelium, to a cell line derived from a mouse immunized with cells bearing a prostate-specific antigen, or derivative thereof and to methods for detecting prostate carcinoma. Frankel et al. teach mouse monoclonal antibodies 24

and 35 on pages 903-907, which are specific for membrane-associated antigens present on human prostatic cancer and normal prostatic epithelium produced by hybridomas resulting from fusion of cells from animals immunized with membrane fractions from prostatic tissue. The mouse myeloma fusion partner used for producing hybridomas is not specified but hybridomas produced using any non-Ig-secreting line would be inherently the same as that claimed in claim 11. Frankel teaches a method for immunohistological detection of cells expressing target antigen in prostate tissue using monoclonal antibody. The method would inherently detect prostate cancer cells expressing the antigen. The claims appear to be the same as or similar to the Frankel reference and are said to be anticipated by Frankel et al. If there are, in fact, differences between the claims and the reference, the reference would have reasonably suggested making the claimed antibodies to one of ordinary skill in the art, making the claimed invention prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made based on the teaching of Frankel et al. that monoclonal antibodies targeted to prostate-specific membrane-associated antigens would be useful for diagnosis and therapy of human prostatic carcinomas. MAB 35 is shown to stain ductal epithelium in hypertrophic tissue and would inherently be expected to stain ductal epithelial in normal or neoplastic tissues with which it is also shown to bind, absent evidence to

the contrary. Heterogeneous staining of tissues would be expected in those tissues manifesting heterogeneous antigen expression, a property which is characteristic of virtually all human cancers. The reference is silent as to the ability of MAB 24 to react with ductal epithelium. The reference is silent as to whether the membrane-associated antigen is non-secreted. Absent evidence to the contrary the reference reads on the claimed antibodies.

27. Claims 1-3, 5, 7-11, 16, 17,19-23 28, 29 and 31 are rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103 as obvious over Webb et al..

Claims 1-3, 5, 7-11 16, 17, 19-23, 28, 29 and 31 are drawn to monoclonal antibodies specific for a membrane-associated, non-secreted antigen of human normal and prostatic cancer epithelium, which can bind to and stain prostatic epithelium and which stains the periphery of cells heterogeneously, weakly stains normal prostatic cells and nonmalignant ductal epithelium and which are of the class IgG. Also claimed are antibodies which are produced by a cell in an animal immunized with metastatic lesions or cells isolated therefrom, including cell line LNCaP, processes for producing the monoclonal antibodies described above, continuous cell lines producing the monoclonal antibodies and methods for detection of prostate carcinoma. Webb et al. teach on pages 7-17 a mouse monoclonal antibody alpha-Pro 13 which is an IgG antibody specific for a membrane-associated, non-released

antigen present in ductal epithelium of prostate tissue and which binds to cancerous and normal prostate epithelium in immunohistological staining assays. The antibody of the reference is produced by a continuous cell line produced by the fusion of a mouse myeloma cell line with splenic lymphocytes isolated from an animal (mouse) immunized with a mixture of viable cells including LNCaP and DU145 both of which are cell lines established from human prostatic cancer metastases. The non-Ig-secreting myeloma SP2/0-Ag14 used for the preparation of the hybridoma is functionally equivalent to that claimed in claim 13 and the resulting hybridoma cell lines produced using either myeloma are inherently the same. The reference indicates on page 11 that heterogeneity is observed in staining of ductal epithelium and that both tumor and putatively normal tissues are stained to varying degrees ranging from weak to strong. The reference teaches an immunohistochemical method for detecting malignant prostate cells in tissue. Thus, the claimed inventions appear to be the same as or similar to those disclosed by the reference and are said to be anticipated by Webb et al. If, in fact, there are differences between the claims and the reference, the reference would have reasonably suggested to one of ordinary skill in the art, making the claimed cell lines and monoclonal antibodies which are specific for membrane-associated, non-released prostatic epithelial antigen making the claimed invention prima facie obvious to one of ordinary skill in the art

at the time the invention was made. One would have been motivated to make the claimed antibodies based on the teaching of the reference that antibodies specific for surface-expressed antigens having organ-restricted distribution would be useful for therapy.

28. Claims 1-6, 10-14 and 20-22, 28, 29, and 30 are rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103 as obvious over Finstad et al..

The above listed claims are drawn to cell lines and the corresponding monoclonal antibodies which have the characteristics described in Items 22 and 23, above, and which are further capable of differentiating prostatic carcinomas from other carcinomas and from certain other normal tissues as specified in claims 4 and 12 and to detection methods. Finstad et al. describe a mouse monoclonal antibody S27, on pages 2955-2959, which is a mouse IgG1 antibody with specificity for a membrane-associated antigen present on normal and malignant human prostate epithelium. The antibody of the reference would be expected to inherently possess the property of binding to cultured cell lines derived from prostatic carcinomas absent evidence to the contrary. The antibody is shown to distinguish prostatic carcinoma from other carcinomas, including breast and colon adenocarcinomas (see Table 3), and to be non-reactive with normal tissues from skin, testis, ovary, pancreas, thyroid, breast, colon and uterus. The claims appear to be the same as or

similar to the antibody of the reference and are, thus, said to be anticipated by Finstad et al. If, in fact, the claims differ from the reference the reference would have reasonably suggested to one of ordinary skill in the art, making the claimed antibodies which are specific for antigens present on prostate tissue but not other normal tissues, making the claimed invention prima facie obvious to one of ordinary skill in the art the time the invention was made. The reference is silent as to the reactivity of the disclosed antibody with bladder or urethra or to LNCaP cells. Absent evidence to the contrary, the antibody of the reference inherently reads on the claims. The reference is silent with regard to heterogeneity of staining of tissues using the monoclonal antibody. However, since heterogeneity of antigen expression is generally characteristic of virtually all human cancers the antibody would inherently be expected to show heterogeneous staining patterns in cell populations manifesting this property. The reference is also silent with regard to whether the surface antigen recognized by the antigen is non-secreted, however, absent evidence to the contrary, the antibody of the reference reads on the claims. The reference does not detail the production of the mouse monoclonal antibody, however, the reference inherently reads on mouse hybridomas resulting from fusion of commonly used mouse myelomas such as p3x63Ag8.653 and the antibody-producing cell with which the myeloma was fused would inherently have produced a prostate-specific antibody based

on the observed reactivity of the resulting monoclonal antibody.

29. Claims 1-24, 26 and 28-31 are, rejected under 35 U.S.C. 103 as being unpatentable over Campbell and further in view of Wright et al. and further in view of Webb et al. and further in view of Frankel et al.. The above listed claims are drawn to monoclonal antibodies and cell lines with the properties discussed in items 22-24 above, and additionally to antibodies with the characteristics described in claim 12, produced by hybridomas wherein antibody-producing cells were originally obtained from individuals with prostatic carcinoma or animals immunized with LNCaP cells or plasma membranes derived therefrom and screened by the methods of claim 19, to process for producing monoclonal antibodies, to the hybridoma 7E11-C5 and monoclonal antibody 7E11 and to methods for detecting prostate carcinoma. Campbell teaches on pages 1-31 that techniques for the preparation of monoclonal antibodies were well known in the art at the time the claimed invention was made. Campbell further teaches on pages 66-85 and 31-66 that it was routine to prepare hybridomas using antibody-producing cells isolated from immunized rodents or from humans. Campbell teaches on page 75 that a number of mouse cell lines were available which would serve as suitable fusion partners, including P3-X63/Ag8. Campbell does not teach monoclonal antibodies having the particular claimed specificities. However, Frankel et al. and Wright et al. teach on pages 903, 5509, respectively, that it was well known to

prepare of monoclonal antibodies specific for membrane-associated antigens present on prostatic epithelium from normal and neoplastic tissues and that it was well known to use a variety of immunogens to elicit antibodies with the described specificities, including live cultured cells or membrane-enriched fractions of tissue culture cell lines (such as the LNCaP or DU-145 cell lines established from prostatic carcinoma metastases) or cells isolated from human tissues. Wright et al. teach a monoclonal antibody D83.21, on page 5509, which is specific for prostatic carcinoma epithelial cells. Immunoperoxidase staining of tissues using D83.21 shows that staining was localized in the membrane as well as in the cytoplasm. D83.21 does not react with normal tissues including bladder, colon, pancreas, breast and testes nor with many other carcinomas tested. The antibody D83.21 taught by Wright et al. is not shown to have the precise reactivities with various tissues and cells as are shown in the specification for the claimed antibodies. For example, MAb D83.21 is shown not to bind to normal or hyperplastic prostatic epithelial cells in immunohistochemical staining assays whereas the specification discloses that MAb 7E11 weakly stains normal epithelial cells. It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to prepare monoclonal antibodies which have specificities for membrane-associated, non-secretory epithelial antigen found prostate and which can discern between prostatic

carcinoma and other carcinomas and which are not reactive with normal tissues, in view of the teachings of Wright et al. or Frankel et al. that antibodies possessing a high degree of specificity for prostate would be useful for diagnosis and/or therapy of prostatic carcinoma. One would have been motivated to select for antibodies which did not bind or which weakly bind antigens present on normal prostatic epithelium in view of the teaching of Wright et al. that antibodies having such a property would have clinical applicability for identification of prostate tumor cells in biopsy specimens. One would have been motivated to select antibodies which bind to membrane-associated antigens in view of the teaching of Frankel et al. that membrane-associated antigens would be superior targets for antibodies intended for in vivo diagnostic or therapeutic use or for detection of prostatic carcinoma metastases. One or ordinary skill would have been motivated to select for antibodies specific for non-secreted antigens since it was well known that circulating antigen can bind to therapeutically administered antibodies and decrease localization of antibody to target tissues, thereby decreasing effectiveness of diagnosis or therapy. One would have had a reasonable expectation of success in isolating antibodies with the claimed specificities based on the teachings of Wright et al. that antibodies were known which could distinguish prostatic carcinomas from other carcinomas and which did not react with normal tissues.

It would have been obvious to prepare hybridomas secreting the claimed antibodies by processes conventional in the art and to screen for hybridomas secreting the desired antibodies using any standard assay technique. It would have been obvious to prepare hybridomas using antibody-producing cells isolated from an individual with prostatic carcinoma or from rodents immunized with prostate-specific antigen. One of ordinary skill in the art would have used any cells or antigenic fractions thereof which express prostate-specific antigens, as immunogens for the production of antibodies specific for prostate antigens. It would have been obvious to use membrane fractions as immunogens in order to partially enrich the immunogenic preparation for membrane antigens against which antibody specificity was desired. One of ordinary skill would have used metastatic lesions as immunogens for the production of the claimed antibodies based on the teaching of Frankel et al. that cells isolated from human sources would be superior to cultured cells as immunogens since antigenic makeup of cultured cells is known to change during prolonged culture. Frankel et al. teach that antibodies could be used for detection of metastatic cells of prostatic carcinoma. One of ordinary skill would have used metastatic cells to elicit the production of antibodies to be used for the detection of prostatic carcinoma metastases, since it was not known whether antigenic expression of primary tumors and metastatic cells is identical, and, therefore, antibodies elicited against metastatic

cells would potentially have greater specificity for the intended use. It would have been obvious to use the claimed antibodies to detect the target antigen in tissues or in serum as exemplified by Frankel et al. or Wright et al.. Even if the claimed monoclonal antibodies per se were distinguishable over the prior art of record, the claimed processes for preparing and using monoclonal antibodies are conventional and obvious over the prior art of record absent a preponderance of evidence of the unobviousness of applying these conventional methods to the claimed monoclonal antibodies and hybridomas (In re Durden 763F.2d 1406 226 USPQ 359).

26. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Paula Hutzell, Ph.D. whose telephone number is (703) 557-1095. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 557-0664.

Hutzell
2/8/90

MARGARET MOSKOWITZ
SUPERVISORY
PATENT EXAMINER
ART UNIT 186